March 16, 2007

Christopher Cleet
Manager, FND Panel
American Chemistry Council
1300 Wilson Boulevard,
Arlington, VA 22209

Dear Mr. Cleet:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the revised test plan and robust summaries for the Fatty Nitrogen Derived Amides (FND Amides) dated September 16, 2004. EPA posted the submission on the ChemRTK HPV Challenge Program Web site on October 18, 2004. The submission is one of five revisions in response to EPA comments dated June 27, 2002 on the original submission dated December 19, 2001. The other four revisions--FND Imidazoline Derivatives, FND Amphoterics, and two single chemicals--will be reviewed separately.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize a chemical for further work.

The FND Amides category is divided into three subcategories:

Fatty Acid Amides (3 sponsored substances),
Fatty Alkanolamides (9 sponsored substances), and
Fatty Acid Reaction Products with Amines (7 sponsored substances).

Data for three supporting chemicals were also submitted: hydrogenated tallow amides (CAS No. 61790-31-6); , N,N-bis(hydroxyethyl)amides C12-18 (CAS No. 68155-06-6); and fatty acids, tall-oil reaction products with polyalkylenepolyamines, dodecylbenzene-sulfonates (CAS No. 68910-87-2).

EPA has reviewed this submission and has reached the following conclusions:

The submitter supports the grouping of the sponsored substances on the basis of their surfactant properties and divides the category into subcategories based on common structural features. The submitter expects the properties of the sponsored chemicals will not be significantly affected by the length of the alkyl chain in the amides or the functional groups that are bound to the amide group. The submitter proposes to satisfy certain endpoints by reading across within and between the various subcategories.

The submitter's approach contains serious flaws, and the sponsored chemicals in FND Amides Subcategories 1-3 cannot be reviewed in the context of a common category because the category definition is too broad and the chemical structures are too diverse. When reading the test plan, it is frequently difficult to determine when the submitter is referring to the entire category or to one of the subcategories. Specifically, the subcategories are defined around significant structural differences between the subcategories, including differences in the strength of the hydrophilic groups, differences in molecular weight and the presence of amine functional groups in only one of the subcategories. These differences and their effects on the physicochemical properties, fate, and toxicities of the sponsored chemicals have not been recognized or accounted for in the test plan. Further, the submitter has provided few or no data to support the claim that chemicals in different subcategories are likely to have similar properties; from their

diverse structures, it is not apparent that they will. It appears more useful and less confusing to submit the current subcategories as separate, free-standing categories. If that is done, several issues will still need to be addressed for two of the groupings. These are described in the following paragraphs.

Subcategory 2. Fatty Alkanolamides

Grouping these sponsored chemicals into a category is reasonable on the basis of similar structures, with one exception: coco fatty acids, compounds with diethanolamine (CAS No. 61790-63-4). This chemical is a salt, not an amide (see table of structures in the test plan), and will have significantly different properties than the amides. Furthermore, diethanolamine is significantly more toxic than other sponsored chemicals in this proposed category.

The most significant difference among the remainder of the category members is in the number of hydroxyethyl groups: ethanolamides contain one hydroxyethyl group and diethanolamides contain two. This difference in the hydrophilic ends of the molecules will alter their surfactant properties. Any differences in the mammalian and aquatic toxicities between these two structural types should be characterized in the test plan. It is not appropriate to assume that they will be similar without supporting data.

Subcategory 3. Fatty Acid Reaction Products with Amines

Five of the seven sponsored chemicals in this category are “reaction products” with incompletely characterized structures. It is therefore difficult to determine their potential similarities. The sponsor needs to provide more information about the typical compositions of these sponsored chemicals and discuss the significance of any differences between them. In particular, more information is needed for the reaction products, including their average molecular weights, and the typical numbers of amine and amide groups. These parameters are important for characterizing the physicochemical properties, fate, and toxicities of the sponsored chemicals. For example, differences in molecular weight due to variable numbers of fatty amide groups may lead to differences in bioavailabilities. In addition, the number and placement of the amines and amides will affect the surfactant properties of the sponsored chemicals, which will influence their toxicities to aquatic organisms. The amine functional groups may induce toxic effects in mammals; therefore differences in the number of amines present in the sponsored chemicals may be toxicologically significant.

Additionally, it seems questionable to include N,N’-ethylenebis(octadecanamide) (CAS No. 110-30-5) and N-[3-(dimethylamino)propyl]cocoamides (CAS No. 68140-01-2) in the same category with the five reaction products. Ethylenebis(octadecanamide) is a very hydrophobic molecule that contains no amines. Read-across from this chemical to the potentially more hydrophilic, amine-containing chemicals in the proposed category does not appear appropriate because of the structural differences and is not supported by the limited data presented. N-[3-(Dimethylamino)propyl]cocoamides is the only substance in the group that can contain only monoamide, and thus is likely to have a significantly lower molecular weight than the rest of the proposed members. Because of its smaller size, it may be more bioavailable than the other members. Its surfactant properties and amine functional group will also be of toxicological importance and it may behave significantly differently than the other members.

The analog chosen by the sponsor to support this subcategory (an alkylbenzene-sulfonic acid salt) also is not appropriate. The alkylbenzenesulfonate anion is a strong surfactant of a completely different structural type than the sponsored chemicals in the proposed category. Any measured data for the analog will be affected by the presence of this counter-ion, and therefore will not be valid for comparison to the other proposed category members.

In conclusion, the FND Amides Category cannot be reviewed in the context of a single category for four primary reasons: 1) the sponsored chemicals within the proposed category are

of diverse chemical structural types and the submitter has not accounted for the effects that these structural differences will have on the properties of the sponsored chemicals; 2) the submitter has not provided enough data to support a read-across strategy between chemicals within each of two subcategories; 3) several of the category members are inadequately characterized; and 4) several sponsored substances do not fit subcategories to which they have been assigned. The subcategories defined by the submitter need to be considered as separate categories. Therefore, EPA reserves judgment on any proposed testing until the sponsored substances can be clarified and the test substances clearly identified.

EPA will post this letter on the HPV Challenge Web site within the next few days. We ask that the Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission. Please send electronic revisions or comments to the following e-mail address: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact me at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Mark Townsend, Chief
HPV Chemicals Branch

cc: O. Hernandez
C. Augustyniak
J. Willis